Lecture 12 ***BONE MARROW FAILURE*** by Dr.Alaa Fadhil

DEFINITION

Pancytopenia due to the failure of bone marrow to produce blood cells

CAUSES OF BONE MARROW FAILURE

Approach:

Pancytopenia

1.Consider causes of peripheral destruction: hypersplenism, sepsis, immune...
Typically, these will be associated with a hypercellular marrow

2. Perform bone marrow investigation

a. Hypercellular marrow

* bone marrow infiltration
-hematologic maligancies(leukemias,myeloma,lymphoma)
-carcinoma
-storage disorders

* myelodysplastic syndromes

* B12 or folate deficiency

b. Hypocellular marrow

* aplastic anemia – congenital - Fanconi's anemia – acquired - idiopathic
- drugs/chemicals – radiation - viruses

A practical approach
pancytopenia
search for:
meds hx
o/e spleen
sepsis
order retics, B12/folate, ANA, SPE, abdo U/S
do bone marrow aspirate and biopsy

hypocellular	hypercelluar
aplastic anemia	hypersplenism
	MDS
	B12 def.
	Myelofibrosis

INHERITED APLASTIC ANEMIA

Inherited variants of aplastic anemia are rare. The most common (approximately two-thirds of cases) is Fanconi's anemia, which is associated with increased chromosomal instability. Less common variants include Schwachman-Diamond syndrome (pancreatic insufficiency with pancytopenia) and dyskeratosis congenita. It is important to differentiate congenital aplastic anemia (ie, present at birth), which can be either inherited or acquired, from inherited (also called constitutional) aplastic anemia, which may be present at birth or may not become evident until years later.

Fanconi's Anemia

Fanconi's anemia is inherited as an autosomal recessive trait.

Physical Abnormalities in Fanconi's Anemia

Skin hyperpigmentation: trunk, neck, intertriginous areas

Short stature

Upper limb abnormalities: thumbs, hands, radii, ulnae

Hypogonadism and genital abnormalities (males)

Other skeletal abnormalities: head, face, neck, spine, lower extremities

Anomalies of eyes, eyelids, or epicanthal folds

Renal abnormalities

Diagnosis

The main diagnostic test is culturing the patient's lymphocytes in diepoxybutane or mitomycin C and demonstrating increased chromosomal instability

Treatment

The treatment of choice for patients with Fanconi's anemia and pancytopenia is allogeneic bone marrow transplant, preferably from a human leukocyte antigen HLA-identical sibling.

Schwachman-Diamond Syndrome

The Schwachman-Diamond syndrome is an inherited disorder characterized by exocrine pancreatic deficiency, pancytopenia, skeletal changes, and others. Inheritance is autosomal recessive. The cause is unknown, but chromosomal fragility is not increased. Patients with Schwachman-Diamond syndrome also are predisposed to developing myelodysplasia and acute leukemia.

Dyskeratosis Congenita

Dyskeratosis congenita consists of mucocutaneous abnormalities with variable hematologic disorders. The mucocutaneous changes include reticulated pigmentation of skin in the upper body, mucosal leukoplakia, and dystrophic changes in the nails. The inheritance pattern appears to be variable; the majority are X-linked. Chromosomal fragility is not increased. The mucocutaneous changes appear in all patients, usually before the age of 10 years. Aplastic anemia occurs in approximately half of patients, usually in their teens. Patients with dyskeratosis congenita also have an increased risk of malignancy.

ACQUIRED APLASTIC ANEMIA

Acquired aplastic anemia can be due to a variety of causes. Important examples include chemicals, drugs or medications, infections, and pregnancy. However, at least half of cases are idiopathic, in which no underlying cause can be found.

Causes of Acquired Aplastic Anemia

1.Ionizing Radiation

2.Chemicals:Benzene is the chemical that has been most closely tied to aplastic anemia. Benzene and its metabolites bind to DNA, inhibit DNA synthesis, and induce strand breaks. Aplastic anemia may develop long after the exposure has stopped..

3.Drugs and Medications:Drugs can cause aplastic anemia in two ways: an expected dose-related aplasia and an unexpected idiosyncratic reaction. The first type of reaction will occur in anyone, given a sufficient amount of the medication. The second type of reaction is rare, occurring in only a small proportion of people given the medication, and can occur with small doses. Cancer chemotherapy drugs are the most common causes of expected dose-related aplastic anemia. Virtually all chemotherapy drugs cause bone marrow suppression as an inevitable result of their cytotoxic effect; however, the effect is transient and reversible.

A wide variety of medications have been associated with aplastic anemia of the idiosyncratic type. The best documented examples are chloramphenicol and phenylbutazone. Other medications that have been implicated include gold compounds, sulfonamides (trimethoprimsulfamethoxazole) and other antibiotics, nonsteroidal anti-inflammatory drugs, antithyroid and anticonvulsant medications

4.Viral Infections: The strongest association is with hepatitis.

5.Miscellaneous :Aplastic anemia has been reported in pregnancy. Completion or termination of the pregnancy is usually followed by hematologic recovery. Aplastic anemia has occasionally been reported in tuberculosis.Other causes include autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, diffuse eosinophilic fasciitis), thymoma, hypogammaglobulinemia, immune thyroid diseases, and transfusion-related graft-versus-host disease (GVHD).

6.Idiopathic :Despite extensive evaluation, no underlying cause can be found in at least half of the cases (idiopathic aplastic anemia). It is now clear that immunemediated suppression of hematopoiesis is responsible for most cases of

idiopathic aplastic anemia

Definition: A disorder characterized by pancytopenia with a hypoplastic marrow, without evidence of marrow involvement with hematologic or non-hematologic neoplastic cells.
Incidence: Aplastic anemia is an uncommon disorder with an incidence of 1-6 per million in Europe and North America; but it is higher in Asian populations.
Etiology: In 50% of cases, no cause can be identified.
Drugs/chemicals:phenylbutazone, chloramphenicol, benzene (idiosyncratic) busulphan, other cytotoxic drugs (dose-dependent)
Radiation (dose-dependent)
Viruses: Hepatitis C, CMV, EBV, HIV
Need to rule out congenital causes such as Fanconi's anemia
Aplastic anemia can be due to
1. Damage to stem cells ("the seeds")
2. Damage to the bone marrow stroma ("the soil"), or
3. A perturbation of the cytokines and other biological response modifiers in the marrow environment.
Most commonly, it is appears to be due to a stem cell defect.
Clinical and laboratory features: Symptoms are due to pancytopenia and are dependent on the severity of the pancytopenia. There is no lymphadenopathy or splenomegaly. There is normocytic or macrocytic anemia. The bone marrow is hypocellular, without evidence of other disorders.
Course: The course is variable, depending on the severity. Those with very severe aplastic anemia (neutrophils $< 0.2 \times 10^9$/L) have a median survival of less than 1 year with supportive care only (transfusions, antibiotics as needed). Death is usually due to infection.
Treatment: If no secondary cause of aplastic anemia is identified, then treatment of idiopathic aplastic anemia depends on the severity. For severely affected young patients, the options are allogeneic bone marrow transplant or immunosuppression (with cyclosporin or anti-thymocyte globulin) if a HLA-matched sibling donor is not available.